UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,641	08/30/2001	Philip A. Beachy	JHUC-P01-017	9388

28213 7590 06/14/2005

DLA PIPER RUDNICK GRAY CARY US, LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,641	BEACHY ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,8-23 and 26-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,8-23 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Claims 2, 3, 6, 7, 24, 25 and 33-52 are cancelled.

The amendment to claims 1, 9, 27, 28 and 32 has been made of record.

Claims 1, 4, 5, 8-23 and 26-32 are pending and are under examination.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Response to Arguments

The objection to the specification is withdrawn in view of Applicant's amendment to the specification, filed on 3/17/2005.

Information Disclosure Statement

Applicant states that a corrected IDS Form 1449 with the correct listing of Sommers, et al. has been attached. However, there is no corrected IDS in the record.

Claim Rejections - 35 USC § 112, second paragraph

Applicant's arguments, see Remarks, filed 3/17/2005, with respect to rejection under 35 U.S.C. § 112, second paragraph have been fully considered and are persuasive. The rejection of claims 1,4,5,8-18 under 35 U.S.C. § 112, second paragraph has been withdrawn.

Claim Rejections - 35 USC § 102

The rejection of claims 1,4,5, 8-25, 27, 29-32 rejected under 35 U.S.C. 102(a) is withdrawn in view of Applicant's amendment of the claims. However, upon further consideration, a new ground(s) of rejection is made in view of Sommers et al (IDS, Biochemistry 39:6898-6909, 2000).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1,4,5, 8, 19 -27, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommers et al (IDS, Biochemistry 39:6898-6909, 2000) in view of Herrick-Davis et al. (IDS, J. Neurochem. 69: 1138-1144, 1997).

The claimed invention is drawn to method of identifying constitutive mutations of a candidate receptor or ion channel comprising providing a library of coding sequences for potentially activating mutations of a G protein coupled receptor, expressing the

library in a mammalian host cell, measuring the activity of the encoded receptor or ion channels either directly by measuring the level of second messengers generated in response to the receptor or ion channel. The claimed invention is further drawn to identifying the coding sequence responsible for at least 2, 5 or 10 fold activation of the receptor or ion channel and to replacing these large side-chain amino acids with small or medium side-chain amino acids are located in or proximate transmembrane segment(s) of the receptor or ion channel.

Sommers et al. teach a method for identifying constitutively activating mutations by making a library carrying random as well as site directed mutations in the amino terminus and transmembrane regions of the STE2 gene (page 6899, left column, 2nd paragraph) in yeast and then screening for these mutations for the receptor activation. Sommers et al. teach using either a direct method of binding 3H-[Nle12]α-factor to STE2 or an indirect method of monitoring a heterologous reporter system by combining the E.coli β-galactosidase gene (lacZ) under the yeast FUS1 promoter activated via the pheromone response pathway. Sommers et al. teach deleting the endogenous STE2 gene and providing external STE genes encoding several mutants of α-factor receptor to study the effects of various antagonists and agonists and to find out the amino acids responsible for switching a receptor between active and inactive stages (page 6898, right column, 1st paragraph). Sommers et al. teach that introduction of mutations in an α-factor receptor (a yeast G protein coupled receptor) constitutively activate the receptor 2, 5, 7 (page 6902, left column, 2nd paragraph and right column, middle of the

first paragraph), or 20 fold (page 6903, right column, 2nd paragraph). Sommers et al do not teach the host cell as a mammalian cell.

Herrick-Davis et al teach application of site directed mutagenesis to substitute amino acids with longer side chains or of different polarity with aromatic substitutions. They teach that the third transmembrane loop of the serotonin receptor (a G protein coupled receptor) is important for the inactivation state of the receptor. Herrick-Davis et al. teach that the mutation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT_2c receptor activates the receptor. Herrick-Davis et al. teach that the 5-HT_2c receptor mutants are expressed in mammalian expression vector pcDNA3 expression by transfecting the plasmid DNA into E. coli (page 1139, left column, last paragraph). They further teach transient transfection of COS7 (monkey kidney cell) cells with a mammalian expression vector (pcNDA3) and measurement of the hydrolysis of phosphotidylinositol as a result of activation from the serotonin receptor via a second messenger pathway (page 1139, left column, second and third paragraph, right column, last paragraph). Herrick-Davis et al. teach a 3 fold (S312K mutation) and a 30 fold (S312F mutation) increase in the binding affinity of 5HT to the mutant receptor (page 1140, left column, 3rd paragraph).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to construct a library of coding sequences for potentially activating mutations in the amino terminus or transmembrane regions as taught by either Sommers or Herrick-Davis. One of ordinary skill in the art at the time of invention was made would have found it prima facie obvious to have expressed the

library in a host cell and to have measured the activity of the mutant receptor using the direct methods taught by Herrick-Davis. The person of ordinary skill in the art would have been motivated do so with a reasonable level of success to more efficiently study the effect of various mutations in side chain amino acids, within the residues of helical domain or the interfaces between transmembrane helices as taught by Sommers for constitutive activation of the receptor in order to increase the probability of finding novel therapeutic agents for antagonist, inverse agonist as taught by Herrick-Davis et al (page, 1139, left column 2nd paragraph).

Claims 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al. as applied to claims 1,4,5, 8, 19 -27, 29-32 above, and further in view of Barak et al (U.S. Patent No. 5,891,646).

The claimed invention is drawn to method of identifying constitutive mutations of a candidate receptor or ion channel comprising providing a library of coding sequences for potentially activating mutations of a G protein coupled receptor, expressing the library in a mammalian host cell, measuring the activity of the encoded receptor or ion channels by measuring an indicator gene (heterologous reporter gene), wherein the indicator gene is modified by manipulating or replacing the promoter sequence at the natural locus of the indicator gene and wherein the indicator gene is regulated by the receptor or ion channel in the host cell.

The teachings of Sommers et al and Herrick-Davis are summarized as set forth supra. Neither Sommers et al not Herrick-Davis teach using a heterologous reporter system to measure the activity in mammalian system. Barak et al teach using

heterologous reporter system where reporter gene green fluorescent protein is made in fusion with beta arrestin under mammalian promoter control and expressed in cells such as insect cells, plant or animal cells including but not limited to HEK cells, HeLa cell, COS cells and primary cells (column 8, lines5-18). They teach use of various promoters for expressing genes in prokaryotic or eukaryotic cells (column 16, lines 33-67).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to construct a library of coding sequences for potentially activating mutations in the amino terminus or transmembrane regions of a GPCR as taught by either Sommers or Herrick-Davis and measure the activation of the GPCR using heterologous reporter system in a mammalian cell as taught by Barak et al. The person of ordinary skill in the art would have been motivated do so with a reasonable level of success to more efficiently study the effect of various constitutive mutations in a mammalian heterologous reporter system because Barak et al teach using GFP reporter system to measure the activation of a GPCR that can be used to study constitutive mutations for finding novel therapeutic agents for antagonist, inverse agonist as taught by Herrick-Davis.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al and Barak et al, as applied to claims 1, 4, 5,8-27 and 29-32 above and further in view of Lerner et al. (US Patent NO. 6,051386).

Claim 28 is drawn to a eukaryotic cell as a pigment cell capable of dispersing or aggregating its pigment in response to an activated receptor or ion channels.

Sommers et al. in combination with Herrick-Davis and Barak et al teach designing and making mutations within the coding sequences of a candidate G protein coupled receptor for the potential activation of the receptor using a library of coding sequences, and expressing the library in a mammalian host cell to measure the increased receptor activity by measuring a change in stimulus through a second messenger pathway as set forth supra. Sommers et al. in combination with Herrick-Davis and Barak do not teach the use of pigment cells to measure the pigment aggregation or dispersion in a pigment cell.

Lerner et al. teach a method of identifying antagonists or agonists for G-protein coupled receptor using a pigment cell. Lerner et al teach that certain chemicals and hormones make changes in signal transduction pathways that involve G-protein coupled receptors. These signal transduction pathways are reflected through changes in the level of cAMP or other second messengers. They teach that measurement of cAMP (by a direct method) or other messenger (by an indirect method) would facilitate antagonist or agonist identification. They teach that certain chemicals and hormones such as melanocyte stimulating hormone (MSH) and norepinephrine cause pigment dispersion, whereas, melatonin cause an increase in the pigment aggregation in a frog melanophores (column 11, line 17-24).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to express the library of coding sequences taught by Sommers et al in a pigment cell to facilitate measurement through pigment dispersion and aggregation in response to a change in G-protein activation as is taught by Lerner

et al. The person of ordinary skill in the art would have been motivated do so with a reasonable level of success to more efficiently study the effect of various constitutive mutations in a mammalian pigment aggregation system because Lerner et al teach measuring activation of GPCR through changes in the level of cAMP in a frog melanophore assay.

The rejection of claims1, 4, 5, 8, 10, 19-24, 26, and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al. in view of Dahiyat et al., is maintained. Applicant's arguments have been fully considered but they are not persuasive. Applicant's traversal that neither Herrick-Davis nor Dahiyat suggest combining references to provide a library of coding sequences for potentially activating mutations in a receptor and do not teach measuring receptor activation with an indicator gene. As set forth in the previous office action mailed on 12/15/2004, on page 10, lines 2-4 that Herrick-Davis teach making mutations in a receptor to increase the probability of finding novel therapeutic agents such as antagonist and inverse agonist. Herrick-Davis et al also teach "constitutively active G protein coupled receptors mimic that active conformation of the receptor in their ability to activate second messenger systems in the absence of agonist" (page1138, first paragraph). They teach that constitutive active GPCRs provide unique model system for studying the active conformation of the receptor involved in G protein coupling, and for testing drugs for their ability to enhance or inhibit constitutive second messenger activation (page 1143, last paragraph).

Applicant argues that Herrick-Davis et al does not teach using library of coding sequences and also do not use measuring the receptor activation with an indicator gene. Herrick-Davis use site directed mutagenesis to substitute amino acids with longer side chains or of different polarity with aromatic substitutions. They teach that the third transmembrane loop of the serotonin receptor (a G protein coupled receptor) is important for the inactivation state of the receptor. Dahiyat et al. teach a method of designing a protein library for the substitution of residues in any part of a protein. They further teach transient transfection of COS7 (monkey kidney cell) cells with a mammalian expression vector (pcNDA3) and measurement of the hydrolysis of phosphotidylinositol as a result of activation from the serotonin receptor via a second messenger pathway.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argues that King teaches heterologous assay in yeast but not in a mammalian cell. Applicant's amendment of claim 1 expressing the library in a

mammalian host cell necessitate new limitations to claims 9-18 and therefore, a new reference of Barak et al is applied. The teachings of Barak et al are as set forth supra.

The rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al in view of Dahiyat et al and King, and further in view of Lerner et al, is maintained. Applicant's arguments have been fully considered but they are not persuasive. Applicant argues that Lerner et al does not discuss expressing a library of coding sequences for potentially activating mutations of a candidate receptor. Herrick-Davis in combination of Dahiyat et al teach expressing a library of peptide sequences for potentially activating mutations as discussed in the previous office action mailed on 12/15/2004.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 572-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gyan Chandra
AU 1646
8 June 2005